REMARKS

I. Status of the Application

Claims 1-46 are presently pending in the application. Claims 20-23 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 1-3, 5, 9, 14, 18, 29-33, 35-37, 39 and 43 stand rejected under 35 U.S.C. § 102(e) as anticipated by Friend et al., U.S. Patent No. 6,203,987. Claims 12, 15-17, 19-22, 24, 27, 28 and 34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Lockhart et al., Nature Biotechnology 14:1675 (1996). Claims 4, 7, 8, 10, 11, 13 and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al., U.S. Patent No. 6,066,457. Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Van Ness et al., U.S. Patent No. 6,248,521. Claims 23, 45 and 46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al., further in view of North et al., U.S. Patent No. 6,114,502. Claims 38, 40 and 42 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Dale, U.S. Patent No. 6,087,112. Claim 44 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al. and North et al., further in view of Dale. Claims 25 and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Scanlon et al., U.S. Patent No. 5,814,489.

II. The Rejections of the Claims Under 35 U.S.C. § 112, Second Paragraph

At page 2, paragraph 3 of the instant Office Action, claims 20-23 and 25 stand rejected under 35 U.S.C. § 112, second paragraph. The Examiner states that claim 23 is indefinite insofar

as it includes the term "complete" While applicants disagree, applicants have deleted the term "complete" from the claim thereby obviating the Examiner's objection.

The Examiner further states that claims 20-22 are indefinite because it is unclear from the claim language as to the active method step or limitation that would lead to the relative expression levels. In response, applicants have amended claims 20-22 to explicitly recite the active step of determining the relative expression levels which applicants believe was already inherent in the claims.

The Examiner also asserts that claim 25 lacks antecedent basis for the phrase "amplified nucleic acids." Applicants have amended the claim to remove "amplified." Applicants therefore respectfully submit that this rejection be reconsidered and withdrawn.

In view of the above, Applicants respectfully request withdrawal of the rejections of claims 20-23 and amended claim 25 under 35 U.S.C. § 112, second paragraph.

III. Claims 1-3, 5, 9, 14, 18, 29-33, 35-37, 39 and 43 Are Novel Over Friend et al.

At page 3, paragraph 4, claims 1-3, 5, 9, 14, 18, 29-33, 35-37, 39 and 43 stand rejected under 35 U.S.C. § 102(e) as anticipated by Friend et al., U.S. Patent No. 6,203,987. The Examiner asserts that Friend et al. teaches gene expression monitoring using a microarray, monitoring the array using hybridization patterns, analyzing a plurality of cells or a single cell, using reverse transcription, using probes between 50 and 2000 bases long, using a solid support, fluorescently labeling probes, using two color fluorescence labeling, probes which are perfectly complementary to the target sequence, tumor diagnostic uses, and using an expression profile. Applicants respectfully traverse the Examiner's rejection.

Friend is directed to enhanced computational methods for analyzing datasets generated from biological samples. While Friend states at col. 5 lines 34-36 that the term "biological sample" is broadly defined to include any cell, tissue, organ or multicellular organism, Friend lacks any teaching of any methods for the creation of datasets generated from single cells or from fewer than 1000 cells.

Applicants respectfully disagree with the Examiner's assertion that the disclosure at col. 1 line 64 that "The profile of a particular cell is therefore typically of high complexity" is a teaching by Friend of the examination of the cellular state of a plurality of cells or a single cell. Instead, that sentence is simply a recognition of the large number of cellular constituents in a cell that are subject to change based on perturbations and, therefore, the difficulty in obtaining meaningful biological response data from a large number of cellular constituents.

Likewise, the Examiner's reference to col. 23 line 29 that "it will be recognized that it is also possible to use cDNA from a single cell and compare, for example, the absolute amount of a particular mRNA in, e.g., a drug-treated or pathway-perturbed cell and an untreated cell" is not a teaching by Friend of the examination of the cellular state of a single cell or fewer than 1000 cells. Applicants respectfully submit that the Examiner's citation must be read with the passage immediately above (col. 23 lines 23-28) which discusses comparing "two cell states". The passage does not disclose using a single cell for each cell state. All Friend states in the next sentence is that "it is possible to use cDNA from a single cell" to compare mRNA in perturbed and untreated states. Applicants respectfully submit that Friend is referring to the possibility to use cDNA from a ***single cell state***. Friend is not suggesting that cDNA be isolated from a single cell, and certainly Friend provides no teaching of how to isolate cDNA from a single cell.

Friend provides only one example where RNA is extracted from cells. In col. 41 lines 34-39, Friend grows yeasts cells to an OD_{600} of 1.0 (±0.2) and then breaks the cells to obtain the total RNA. Applicants respectfully submit that the amount of yeast cells grown by Friend based on the optical density is several orders of magnitude larger than the less than 1000 cells of claim 1. Applicants were the first to analyze the gene expression characteristics of fewer than 1000 cells and even of a single cell. Applicants invention is a very significant advance over gene expression methods using microarrays such as Friend that use cells on the order of a million or more from which to extract cellular material.

IV. Claims 12, 15-17, 19-22, 24, 27, 28 and 34 Are Patentable Over Friend et al. In View of Lockhart et al.

At page 5, paragraph 2, claims 12, 15-17, 19-22, 24, 27, 28 and 34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al., U.S. Patent No. 6,203,987 in view of Lockhart et al., Nature Biotechnology 14:1675 (1996). The Examiner states that it would have been *prima facie* obvious to apply the array of Lockhart et al. to the method of expression monitoring and classification of Friend et al. in order to classify the many different genes in the human body simultaneously. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Lockhart et al. fails to cure the deficiencies of Friend.

Accordingly, Applicants respectfully request that rejection of claims 12, 15-17, 19-22, 24, 27, 28 and 34 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

V. Claims 4, 7, 8, 10, 11, 13 and 41 Are Patentable Over Friend et al. In View of Hampson et al.

At page 6, paragraph 1, claims 4, 7, 8, 10, 11, 13 and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al., U.S. Patent No. 6,066,457. The Examiner states that it would have been *prima facie* obvious to apply the method of producing short cDNA molecules of Hampson et al., with the differential expression of Friend et al. in order to obtain a representative sample of original mRNAs for accurate gene expression. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Hampson et al. fails to cure the deficiencies of Friend. Accordingly, Applicants respectfully request that rejection of claims 4, 7, 8, 10, 11, 13 and 41 under the 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VI. Claim 6 Is Patentable Over Friend et al. In View of Van Ness et al.

At page 6, paragraph 3, claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Van Ness et al., U.S. Patent No. 6,248,521. The Examiner states that it would have been *prima facie* obvious to apply the partial cDNA sequences of Van Ness et al., with the array of Friend et al. in order to directly compare the expression of different cell types. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Van Ness et al. fails to cure the deficiencies of Friend. Accordingly,

Applicants respectfully request that the rejection of claim 6 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VII. Claims 23, 45 and 46 Are Patentable Over Friend et al. In View of Hampson et al., Further In View of North et al.

At page 7, paragraph 3, claims 23, 45 and 46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al., further in view of North et al., U.S. Patent No. 6,114,502. The Examiner states that it would have been *prima facie* obvious to study the expression of the TULP sequences of North et al., with the array of Friend et al. in order to identify the cells that express the sequences for diagnostic and therapeutic purposes. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Neither Hampson et al. nor North et al. Van Ness et al. fail to cure the deficiencies of Friend. Accordingly, Applicants respectfully request that the rejection of claims 23, 45 and 46 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

VIII. Claims 38, 40 and 42 Are Patentable Over Friend et al. In View of Dale

At page 8, paragraph 2, claims 38, 40 and 42 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Dale, U.S. Patent No. 6,087,112. The Examiner states that it would have been *prima facie* obvious to study cell differentiation as taught by Dale with the array of Friend et al. in order to identify the expressed genes during differentiation or apoptosis. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Dale fails to cure the deficiencies of Friend. Accordingly, Applicants respectfully request that the rejection of claims 38, 40 and 42 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

IX. Claim 44 Is Patentable Over Friend et al. In View of Hampson et al. and North et al. Further In View of Dale

At page 8, paragraph 3, claim 44 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Hampson et al. and North et al., further in view of Dale. The Examiner states that it would have been *prima facie* obvious to study cell differentiation as taught by Dale with the array of Friend et al. in order to identify the expressed genes during differentiation as related to neuronal expression of TULP proteins as they were involved in many defects as taught by North et al. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Neither Hampson et al., North et al. nor Dale fail to cure the deficiencies of Friend. Accordingly, Applicants respectfully request that the rejection of claim 44 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

X. Claims 25 and 26 Are Patentable Over Friend et al. In View of Scanlon

At page 9, paragraph 2, claims 25 and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Friend et al. in view of Scanlon, U.S. Patent No. 5,814,489. The Examiner states that it would have been *prima facie* obvious to amplify, cleave and end label fragments with the assay of Friend et al. in order to detect and identify specific mRNAs for gene expression monitoring. Applicants respectfully traverse the rejection.

Applicants claims are directed to novel methods of monitoring gene expression in fewer than 1000 cells. As discussed above, Friend fails to teach or suggest gene expression monitoring in fewer than 1000 cells. Scanlon fails to cure the deficiencies of Friend. Accordingly, Applicants respectfully request that the rejection of claims 25 and 26 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

XI. Conclusion

Having addressed all outstanding issues, applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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Version of Amendments With Markings To Show Changes Made

20. (Amended) The method of claim 9, further including the step of determining relative expression levels of detected genes and wherein the relative expression levels of detected genes vary by at least about [to] 2-fold to about ten-fold.

21. (Amended) The method of claim 9, further including the step of determining relative expression levels of detected genes and wherein the relative expression levels of detected genes vary by at least 100 fold.

22. (Amended) The method of claim 9, further including the step of determining relative expression levels of detected genes and wherein the relative expression levels of detected genes vary by at least 1000 fold.

23. (Amended) The method of claim 1, wherein the probe array [is a complete array comprising] comprises all probes of a given length.

25. (Amended) The method of claim 2, further comprising cleaving [amplified] nucleic acids into fragments.

[42] 43. (Amended) A method of identifying a specific cell type comprising:

determining an expression profile of a plurality of cells;

classifying the cells in clusters determined by similarity of expression profile;

determining the nature and function of a plurality of cells.

[43] 44. (Amended) The method of claim 42 wherein the cells originate from the adult brain.

[44] 45. (Amended) The method of claim 41 wherein the cells originate from peripheral sensory organs.

[45] 46. (Amended) The method of claim 41 wherein one of the plurality of cells can be deduced to have stem cell potentials.